Complete Summary

GUIDELINE TITLE

ASHP therapeutic guidelines for nonsurgical antimicrobial prophylaxis.

BIBLIOGRAPHIC SOURCE(S)

American Society of Health-System Pharmacists. ASHP therapeutic guidelines for nonsurgical antimicrobial prophylaxis. American Society of Health-System Pharmacists. Am J Health Syst Pharm 1999 Jun 15;56(12):1201-50. [377 references]

COMPLETE SUMMARY CONTENT

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INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY

SCOPE

DISEASE/CONDITION(S)

- Infection in specialized settings, including endocarditis in patients at risk who are undergoing dental, respiratory, gastrointestinal (GI), or genitourinary (GU) procedures; nosocomial pneumonia in mechanically ventilated patients; and meningitis after nonpenetrating head trauma associated with a basilar skull fracture
- Infection associated with defined exposures and travel including influenza A in patients at risk; malaria and traveler's diarrhea in persons traveling abroad; tuberculosis (TB); and HIV infection in occupational exposure
- Perinatally acquired infection, including HIV, HSV-2, and group B streptococcal disease
- Opportunistic infections in the immunocompromised host, including afebrile granulocytopenic cancer patients, afebrile bone marrow transplant recipients, and HIV-infected persons.

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Prevention

CLINICAL SPECIALTY

Dentistry
Infectious Diseases
Internal Medicine
Pediatrics
Pharmacology

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Dentists
Nurses
Pharmacists
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To provide practitioners with standardized effective regimens for the rational use of prophylactic antimicrobials.

TARGET POPULATION

Adult and pediatric patients (1 to 21 years of age), including infants (one month to 2 years of age)

INTERVENTIONS AND PRACTICES CONSIDERED

Nonsurgical antimicrobial prophylaxis

Note: For specific pediatric drug therapy refer to recommendations.

Recommended and alternative antimicrobials for primary prophylaxis for the following infections and settings (refer to the guideline document for dosage information and further information):

Bacterial endocarditis; Dental, respiratory tract or esophageal procedure

- Recommended: Amoxicillin
- Alternative: Clindamycin, cephalexin, cefadroxil, azithromycin or clarithromycin, erythromycin

Bacterial endocarditis; Gastrointestinal or genitourinary procedures for patients at moderate risk

- Recommended: Amoxicillin or ampicillin (high risk add gentamicin)
- Alternative: Regimens are suggested in the document

Meningitis, Nonpenetrating head trauma: Not recommended

Nosocomial pneumonia, intensive care unit: Not recommended

Influenza A (in persons at risk)

- Recommended: Amantadine
- Alternative: Rimantadine

Malaria

- Recommended: Chloroquine or mefloquine depending on endemic susceptibility
- Alternative: Doxycycline, or chloroquine with or without chloroguanide, pyrimethamine-sulfadoxine

Traveler's diarrhea: Not recommended

Tuberculosis (TB)

- Recommended: Isoniazid
- Alternative: Isoniazid or rifampin with or without ethambutol; if exposed to multidrug-resistant TB and high likelihood of infection, pyrazinamide with ethambutol or pyrazinamide with a fluoroquinolone (ofloxacin or ciprofloxacin)

Human Immunodeficiency Virus (HIV), percutaneous exposure to blood

- Recommended: Zidovudine plus lamivudine plus either indinavir or nelfinavir

Human Immunodeficiency Virus, other percutaneous exposure or exposure of mucus membranes or skin

- Not recommended
- Alternative (depending on details of exposure): Do not offer or offer zidovudine plus lamivudine

Perinatally acquired HIV

- Recommended: Zidovudine
- Alternative: None

Perinatally acquired HSV-2

- Recommended: Acyclovir

- Alternative: Valacyclovir, or famciclovir

Perinatally acquired Group B streptococcus

- Recommended: Penicillin G
- Alternative: Ampicillin, clindamycin or erythromycin

Opportunistic infection in patients with granulocytopenia or receiving bone marrow transplantation (BMT): Not recommended, refer to guideline document for alternative regimens and additional discussion

Fungal infections in patients infected with HIV: Not recommended, refer to guideline document for alternative regimens and additional discussion

Opportunistic infection in patients infected with HIV:

Disseminated Mycobacterium avium complex

- Recommended: Azithromycin
- Alternative: Rifabutin with or without azithromycin

P. carinii pneumonia (PCP)

- Recommended: trimethoprim (TMP) and sulfamethoxazole (SMX)
- Alternative: Dapsone; dapsone plus pyrimethamine and leucovorin, aerosolized pentamidine

Toxoplasma gondii encephalitis

- Not recommended, refer to guideline document for alternative regimens and additional discussion

Cytomegalovirus (CMV) disease

- Not recommended, refer to guideline document for alternative regimens and additional discussion

Primary herpes simplex virus (HSV)

- Not recommended

Primary varicella zoster virus (VZV)

- Not recommended, refer to guideline document for alternative regimens and additional discussion

MAJOR OUTCOMES CONSIDERED

- Efficacy of primary prophylaxis (prevention of an initial infection)

- Frequency of antimicrobial resistance associated with prophylactic use of antimicrobials
- Intensive care unit (ICU) stay, hospital stay, mortality

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The primary literature from the previous American Society of Health-System Pharmacists (ASHP) Therapeutic Guidelines on Nonsurgical Antimicrobial Prophylaxis was reviewed together with the primary literature published between the date of the previous guidelines and August 1997, identified by a MEDLINE search.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Level I: evidence from large, well-conducted randomized, controlled clinical trials or a meta-analysis

Level II: evidence from small, well-conducted randomized, controlled clinical trials

Level III: evidence from well-conducted cohort studies

Level IV: evidence from well-conducted case-control studies

Level V: evidence from uncontrolled studies that were not well conducted

Level VI: conflicting evidence that tends to favor the recommendation

Level VII: expert opinion

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not applicable

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

These guidelines were prepared by the Rocky Mountain Poison and Drug Center under contract to the American Society of Health-System Pharmacists (ASHP). The project was coordinated by a drug information pharmacist who worked with a multidisciplinary consortium of writers and consulted with six physicians on staff at the University of Colorado Health Sciences Center. The project coordinator worked in conjunction with an independent panel of eight clinical pharmacy specialists with expertise in either adult or pediatric infectious disease. The panel was appointed by ASHP.

Guideline development included consideration of the following characteristics: validity, reliability, clinical applicability, flexibility, clarity, and a multidisciplinary nature as consistent with ASHP´s philosophy on therapeutic guidelines. Recommendations for the use of an antimicrobial are substantiated by the strength of evidence that supports the recommendation.

A category C recommendation represents a consensus of the expert panel based on the clinical experience of individual panel members and a paucity of quality supporting literature. In cases for which opinions were markedly divided, the recommendations indicate that a substantial number of panel members supported an alternative approach.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Each recommendation was assigned a category corresponding to the strength of evidence that supports the use or nonuse of antimicrobial prophylaxis:

Category A: levels I-III

Category B: levels IV-VI

Category C: level VII

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Comparison with Guidelines from Other Groups
External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines underwent multidisciplinary field review to evaluate their validity, reliability, and utility in clinical practice. The final document was approved by the American Society of Health-System Pharmacists (ASHP) Commission on Therapeutics and the ASHP Board of Directors.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Endocarditis

The choice of antimicrobials for bacterial endocarditis prophylaxis is based on the procedure and the patient's level of risk for endocarditis. Dental procedures for which prophylaxis is recommended include dental extractions, periodontal procedures (including surgery, scaling and root planing, probing, and recall maintenance), dental implant placement and reimplantation of avulsed teeth, endodontic (root canal) instrumentation or surgery only beyond the apex, subgingival placement of antimicrobial fibers or strips, initial placement of orthodontic bands but not brackets, intraligamentary local anesthetic injections, and prophylactic cleaning of teeth or implants when bleeding is anticipated. Prophylaxis is optional when there may be substantial bleeding, such as with operative and prosthodontic restorative dentistry, including restoration of decayed teeth (filling cavities) and replacement of missing teeth. Respiratory tract procedures for which prophylaxis is warranted include tonsillectomy and adenoidectomy, surgical operations that involve respiratory mucosa, and bronchoscopy with a rigid bronchoscope. Prophylaxis is optional for high-risk patients undergoing bronchoscopy with a flexible bronchoscope, with or without biopsy. Esophageal procedures include sclerotherapy for esophageal varices and esophageal stricture dilation. Gastrointestinal (GI) procedures include endoscopic retrograde cholangiography with biliary obstruction, biliary tract surgery, and surgical operations that involve intestinal mucosa. Prophylaxis is optional for high-risk patients undergoing transesophageal echocardiography and endoscopy with or without GI biopsy. Genitourinary (GU) tract procedures include prostatic surgery, cystoscopy, and urethral dilation. Prophylaxis is optional for high-risk patients undergoing vaginal hysterectomy and vaginal delivery. A list of related procedures, such as endotracheal intubation, for which endocarditis prophylaxis is not recommended because of the lesser risk of associated bacteremia can be found in the American Heart Association (AHA) guidelines. Patients who take an oral penicillin for secondary prophylaxis are often colonized by penicillin-, amoxicillin-, or ampicillin-resistant viridans streptococci. These patients should receive clindamycin, azithromycin, or clarithromycin instead of penicillin, amoxicillin, or ampicillin.

Dental, respiratory tract, and esophageal procedures in patients at moderate or high risk. The recommended regimen for moderate- or high-risk patients undergoing dental, respiratory tract, or esophageal procedures is amoxicillin 2 g

orally one hour before the procedure. For patients unable to take oral medications, the alternative is ampicillin 2 g (as the sodium) i.v. or i.m. within 30 minutes of the procedure. For patients allergic to penicillin, the alternative is clindamycin 600 mg (as the hydrochloride) orally one hour before the procedure, cephalexin or cefadroxil 2 g orally one hour before the procedure, or azithromycin or clarithromycin 500 mg orally one hour before the procedure. An acceptable alternative is erythromycin 800 mg (as the ethylsuccinate) or 1 g (as the stearate) orally two hours before the procedure and then half the dose six hours after the initial dose. For penicillin-allergic patients and patients unable to take oral medications, the alternative is clindamycin 600 mg (as the phosphate) i.v. within 30 minutes before the procedure or cefazolin 1 g (as the sodium) i.v. or i.m. within 30 minutes of the procedure.

GI and GU procedures for patients at moderate risk. For moderate-risk patients undergoing GI or GU procedures, the recommended regimen is amoxicillin 2 g orally one hour before the procedure or ampicillin 2 g (as the sodium) i.v. or i.m. within 30 minutes of the start of the procedure. For patients allergic to ampicillin or amoxicillin, the alternative is vancomycin 1 g (as the hydrochloride) i.v. over one to two hours (complete infusion within 30 minutes of the start of the procedure). For endoscopic retrograde cholangiopancreatography (ERCP) procedures, a fluoroquinolone such as ciprofloxacin given at a dose of 750 mg (as the base or hydrochloride) orally 60 to 90 minutes before the procedure is considered by some to be an acceptable alternative regimen.

GI and GU procedures for patients at high risk. The recommended regimen for high-risk patients undergoing GI or GU procedures is ampicillin 2 g (as the sodium) i.v. or i.m. plus gentamicin 1.5 mg/kg (as the sulfate; not to exceed 120 mg) i.v. or i.m. within 30 minutes of the start of the procedure followed by ampicillin 1 g i.v. or i.m. or amoxicillin 1 g orally six hours later. For patients allergic to ampicillin or amoxicillin, the alternative is vancomycin 1 g (as the hydrochloride) i.v. over one to two hours (complete infusion within 30 minutes of the start of the procedure) plus gentamicin 1.5 mg/kg (not to exceed 120 mg) i.v. or i.m. (complete injection within 30 minutes of the start of the procedure). For patients undergoing an ERCP procedure, ciprofloxacin 750 mg (as the base or hydrochloride) orally (any fluoroquinolone may be appropriate) given 60 to 90 minutes before the procedure may be considered an acceptable alternative regimen. (Strength of evidence for prophylaxis = B)

Pediatric dosage. The choice of antimicrobials for endocarditis prophylaxis in pediatric patients is based on the procedure and the patient´s level of risk for endocarditis. Readers are referred to the adult recommendations for the choice of antimicrobials. The equivalent pediatric initial doses are oral amoxicillin 50 mg/kg, oral clindamycin 20 mg/kg (as the hydrochloride), ampicillin 50 mg/kg (as the sodium) i.v. or i.m., clindamycin 20 mg/kg (as the phosphate) i.v., gentamicin 1.5 mg/kg (as the sulfate) i.v., and vancomycin 20 mg/kg (as the hydrochloride) i.v. The total pediatric dose should not exceed the total adult dose.

Meningitis after nonpenetrating head trauma associated with basilar skull fracture

Prophylactic administration of antimicrobials to patients with a basilar skull fracture after nonpenetrating head trauma, either with or without cerebrospinal

fluid (CSF) leakage, is not recommended. (Strength of evidence against prophylaxis = C)

Pediatric dosage. Prophylaxis for pediatric patients with a basilar skull fracture after nonpenetrating head trauma, either with or without CSF leakage, is not recommended.

Nosocomial pneumonia in patients receiving mechanical ventilation

Because there is no significant benefit in terms of ICU stay, hospital stay, or mortality, the routine use of selective decontamination in mechanically ventilated patients cannot be recommended. (Strength of evidence against prophylaxis = A)

Pediatric dosage. Selective decontamination is not recommended in mechanically ventilated pediatric patients.

Influenza A

Chemoprophylaxis is not a substitute for vaccination. Practitioners should refer to the Centers for Disease Control and Prevention (CDC) annually for specific vaccine recommendations.

CDC recommends chemoprophylaxis with amantadine or rimantadine against influenza A in persons at risk for developing complications under certain circumstances: (1) persons at high risk who were vaccinated after influenza A activity began, because the development of antibodies can take as long as two weeks, (2) persons providing care to those at high risk who are not vaccinated; prophylaxis should be considered for all employees, regardless of their vaccination status, if the outbreak is caused by a variant strain of influenza A that might not be controlled by the vaccine, (3) persons who have immune deficiency and who are expected to have an inadequate antibody response to influenza vaccine, (4) persons for whom influenza vaccine is contraindicated, including persons who have severe anaphylactic hypersensitivity to egg protein or other vaccine components, and (5) other persons who wish to avoid influenza A illness.

Factors that should be considered before initiation of chemoprophylaxis are cost, adherence, and potential adverse effects. No well-controlled studies of pregnant women have been conducted, and the drug should be used during pregnancy only when the potential benefits outweigh the possible risk to the fetus.

On the basis of cost minimization, the regimen of choice is usually amantadine hydrochloride 100 mg orally twice daily. An alternative regimen is rimantadine hydrochloride 100 mg orally twice daily for persons who cannot tolerate the central nervous system (CNS) adverse effects of amantadine. Prophylaxis should be continued for 10 days after exposure. When an antiviral agent is used in conjunction with the vaccine, prophylaxis should be continued for two weeks after administration of the vaccine. If the vaccine is unavailable or contraindicated, prophylaxis should be continued for the duration of influenza A activity in the community. (Strength of evidence for prophylaxis = A)

Pediatric dosage. Amantadine is the first drug of choice for influenza A prophylaxis; rimantadine is an alternative. Readers are referred to the adult recommendations for the indications to use chemoprophylaxis.

The dosage of amantadine hydrochloride in children of ages one to eight years and in older children who weigh less than 40 kg is 5–9 mg/kg/day orally in two divided doses (up to 200 mg daily). For children 9 to 12 years of age who weigh more than 40 kg, the dosage of amantadine hydrochloride is 100 mg orally twice daily. The dosage of rimantadine hydrochloride in children less than 10 years of age is 5 mg/kg orally once daily (up to 150 mg daily). For children older than 10 years, the dosage of rimantadine hydrochloride is 100 mg orally twice daily. Prophylaxis should be continued for 10 days after exposure to influenza A. When an antiviral agent is used in conjunction with the vaccine, prophylaxis should be continued for two weeks after the last dose of vaccine (one dose is recommended for children older than nine years; two doses of vaccine are required for children up to nine years of age who have not been previously vaccinated). If the vaccine is unavailable or contraindicated, prophylaxis should be continued for the duration of influenza A activity in the community.

Malaria

Nonantimicrobial measures. Implementing measures to reduce the risk of mosquito bites is the nonantimicrobial approach to preventing malaria. Travelers should remain in well-screened areas, use mosquito nets, and wear clothing that covers their entire body. Insect repellents should be used on exposed areas of skin. The most effective mosquito repellent is N,N-diethyl metatoluamide (DEET). DEET-containing repellents should be used according to directions and should be used sparingly on children. Adults should use 30–35% DEET on exposed skin; pediatric preparations containing 6–10% DEET are also available. For current travel recommendations, contact the CDC travel hotline at (888) 232-3299 or (888) 232-3228 or visit http://www.cdc.gov) (select Travelers' Health).

Areas of chloroquine susceptibility. Chloroquine alone is recommended for malaria prophylaxis in areas of chloroquine susceptibility. The adult dosage is chloroquine phosphate 500 mg (300 mg base) once a week initiated one week before entry into the malarious area and continuing for four weeks after departure from the area.

Areas of chloroquine resistance. Mefloquine is recommended for malaria prophylaxis in areas of chloroquine resistance. The adult dosage is mefloquine hydrochloride 250 mg (228 mg base) once weekly beginning one week before travel and continued for four weeks after the person leaves the malarious area. Mefloquine should not be used by travelers with a history of epilepsy, psychiatric disorders, or a known hypersensitivity to mefloquine. An alternative is doxycycline 100 mg (as the calcium, hyclate, or monohydrate) daily beginning one day before travel and continued for four weeks after the person leaves the area. Doxycycline should not be used by pregnant women. Another alternative is chloroquine phosphate (same dosage as previously described) with or without chloroguanide hydrochloride (proguanil) 200 mg/day during exposure and for four weeks after last exposure plus combination tablets of pyrimethamine (25 mg/tablet) and sulfadoxine (500 mg/tablet) as presumptive treatment—three tablets for febrile

illness when medical care is not immediately available. (Strength of evidence for prophylaxis = B)

Pediatric dosage. Areas of chloroquine susceptibility. Chloroquine is recommended for malaria prophylaxis in children in areas of chloroquine susceptibility. The pediatric dosage is chloroquine phosphate 8.3 mg/kg (5 mg/kg base) orally once a week. The maximum weekly dose is 498 mg of chloroquine phosphate (300 mg base).

Areas of chloroquine resistance. Mefloquine hydrochloride is the drug of choice for malaria prophylaxis in children in areas of chloroquine resistance. The pediatric dosage is mefloquine hydrochloride 5 mg/kg (4.6 mg/kg base) weekly for children weighing less than 15 kg, one quarter of a 250-mg mefloquine hydrochloride tablet per week for children weighing 15–19 kg, half a tablet per week for children weighing 20–30 kg, three quarters of a tablet per week for children weighing 31–45 kg, and one tablet weekly for children weighing more than 45 kg. An alternative is doxycycline 2 mg/kg/day (as the calcium, hyclate, or monohydrate) (maximum daily dose, 100 mg/day) for children older than eight years. Doxycycline should not be used in children less than eight years of age. Another suggested alternative is chloroquine phosphate (same dosage as previously described), with or without chloroguanide hydrochloride 50 mg/day for children younger than 2 years, 100 mg/day for ages 2–6 years, 150 mg/day for ages 7–10 years, or 200 mg/day for children older than 10 years plus combination pyrimethamine (25 mg/tablet) and sulfadoxine (500 mg/tablet) for presumptive treatment (one quarter of a tablet for children younger than 1 year, half a tablet for 1–3 years, one tablet for 4–8 years, two tablets for 9–14 years, and three tablets for children older than 14 years).

Traveler's diarrhea

Prophylaxis of traveler's diarrhea is not recommended. Traveler's diarrhea, even when untreated, is most often mild and transient. The antimicrobials used as prophylaxis against traveler's diarrhea place the otherwise healthy person at unnecessary risk of toxicity and superinfection and encourage the emergence of resistant organisms. A National Institutes of Health consensus panel recommended that travelers who are otherwise healthy not take antimicrobials for the prevention of traveler's diarrhea. In addition, CDC does not recommend antimicrobial prophylaxis, focusing instead on prevention of traveler's diarrhea through dietary control. Consumption of boiled, bottled, or chemically disinfected water and avoidance of uncooked fruits and vegetables, unpasteurized dairy products, and raw meat or shellfish are the safest methods for avoiding traveler's diarrhea. Immunocompromised patients may be viable candidates for prophylaxis (trimethoprim–sulfamethoxazole, bismuth subsalicylate, and ciprofloxacin are all effective), but no studies in this population are available. (Strength of evidence against prophylaxis = C)

Pediatric dosage. Prophylaxis of traveler´s diarrhea is not recommended for children.

Tuberculosis (TB)

Official recommendations for the prevention of TB have been published by ACET (Advisory Council for the Elimination of Tuberculosis, Centers for Disease Control and Prevention). The recommendation to start preventive therapy is based on risk factors and skin-test results. Preventive therapy is indicated for the following skin-test results and risk factors:

1. In persons of any age with an induration of greater than or equal to 5 mm who have had recent close contact with persons who have active TB, who have HIV infection or risk factors for HIV infection but unknown HIV status, or who have fibrotic chest radiographs consistent with healed TB.
2. In persons of any age with an induration of greater than or equal to 10 mm who are intravenous drug users known to be HIV seronegative and who have other medical conditions (see risk factors).
3. In persons with an induration of greater than or equal to 10 mm who are residents or employees of high-risk congregate settings (prisons and jails, nursing homes and other long-term-care facilities for the elderly, health care facilities, mental institutions, and homeless shelters), foreign-born persons recently arrived (i.e., within the past five years) from countries with a high prevalence or incidence of TB, some medically underserved, low-income populations (i.e., migrant farm workers, homeless persons), high-risk racial or ethnic minority populations (as defined locally), or infants, children, and adolescents exposed to adults in high-risk categories.
4. In persons less than 35 years of age with an induration of greater than or equal to 10 mm or in persons 35 years of age or older with an induration of greater than or equal to 15 mm who are recent converters (within the past two years).
5. In persons with an induration of greater than or equal to 15 mm who do not meet any of the previous criteria.

The recommended dosage of isoniazid is 300 mg orally daily for six months. An alternative dosage is 15 mg/kg (up to 900 mg) twice weekly for patients who must have therapy directly observed. In patients with immunosuppression or with radiographic abnormalities suggestive of "old" TB, the recommended duration of prophylaxis is 12 months. In patients who cannot take isoniazid because of adverse effects, oral rifampin 600 mg every day with or without ethambutol hydrochloride 15 mg/kg/day may be used. In patients infected with an isoniazid-resistant organism, rifampin with or without isoniazid or ethambutol has been recommended. Prophylaxis with pyridoxine hydrochloride 50 mg daily to prevent peripheral neuritis or convulsions due to isoniazid is generally not necessary, except for persons with conditions in which neuropathy is common (diabetes, uremia, alcoholism, malnutrition), pregnant women, and persons with a seizure disorder. For persons exposed to multidrug-resistant TB and with a high likelihood of being infected (with an induration of 5 mm, anergic, or with HIV infection), oral pyrazinamide 25 mg/kg/day and oral ethambutol hydrochloride 15 mg/kg/day or pyrazinamide and a fluoroquinolone (ciprofloxacin 750 mg twice a day or ofloxacin 400 mg twice a day) for 12 months are recommended. (Strength of evidence for prophylaxis = A)

Pediatric dosage. The recommendation for TB prophylaxis in children is isoniazid 10 mg/kg/day (maximum daily dose, 300 mg) administered as a single daily dose for six months. For children unable to take isoniazid, rifampin 10–20 mg/kg/day (maximum daily dose, 600 mg) in a single daily dose is recommended.

Prophylaxis with pyridoxine hydrochloride 1–2 mg/kg/day to prevent peripheral neuritis or convulsions due to isoniazid is generally not necessary, except for persons with conditions in which neuropathy is common (diabetes, uremia, malnutrition), children or adolescents on meat- or milk-deficient diets, breast-feeding infants, and children with a seizure disorder. For children exposed to multidrug-resistant TB and with a high likelihood of being infected, pyrazinamide 20–40 mg/kg/day with doses given every 12–24 hours (maximum daily dose, 2 g) and ethambutol hydrochloride 15–25 mg/kg/day (maximum daily dose, 2.5 g) should be used. Ethambutol is generally not recommended for children whose visual acuity cannot be monitored. However, ethambutol should be considered for all children with organisms resistant to other drugs when susceptibility to ethambutol has been demonstrated or is likely.

Occupational Exposure to HIV

The best means of preventing HIV seroconversion from occupational exposure is to reduce the likelihood of exposure through the use of standard precautions during procedures and in the handling of blood and other body fluids. In the case of occupational exposure, current guidelines have been proposed by the United States Public Health Service (USPHS) and supported by an international panel. The recommendations are provisional because of limited data on efficacy and toxicity of postexposure prophylaxis and risk for HIV seroconversion after different types of exposure. The recommended dosages are zidovudine 300 mg orally twice daily or 200 mg three times a day, lamivudine 150 mg orally twice a day, and indinavir 800 mg (as the sulfate) orally three times a day or nelfinavir 750 mg (as the mesylate) orally three times a day. Prophylaxis is continued for four weeks.

Alternative regimens with other nucleoside reverse-transcriptase inhibitors, protease inhibitors, or nonnucleoside reverse-transcriptase inhibitors may be required. Postexposure prophylaxis should be initiated promptly, preferably within one to two hours after HIV exposure. Although animal studies suggest that postexposure prophylaxis is not effective when started later than 24–36 hours after exposure, the interval after which there is no benefit from postexposure prophylaxis for humans is undefined. CDC recommends prophylaxis for all high-risk exposures. CDC does not recommend prophylaxis for lower-risk exposures, with the provision that these exposed health care workers be offered the option of receiving prophylaxis. Specific considerations by route of exposure follow.

Percutaneous exposure to blood. When a large volume of blood (e.g., in the case of deep injury with a large-diameter hollow needle that was previously in the source patient´s vein or artery, especially involving an injection of the source patient´s blood) or blood containing a high HIV titer (e.g., if the source patient has acute retroviral illness or end-stage AIDS, in which case viral load measurement may be considered but has not been evaluated in relation to prophylaxis) or both are involved, zidovudine plus lamivudine plus indinavir should be recommended. (These situations are regarded as presenting the highest or increased risk.)

When neither a large volume of blood nor blood with a high titer of HIV (e.g., a solid suture-needle injury from a source patient with asymptomatic HIV infection) is involved, prophylaxis is not recommended. The exposed worker may be offered

zidovudine plus lamivudine. (This scenario is regarded as presenting no increased risk.)

Percutaneous exposure to fluid containing visible blood or tissue. When fluid (including semen, vaginal secretions, and cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids) is involved, prophylaxis is not recommended. The exposed worker may be offered zidovudine plus lamivudine.

Percutaneous exposure to other fluid. When other fluid (e.g., urine) is involved, prophylaxis is not recommended and should not be offered.

Mucous membrane exposure and skin exposure. Regarding skin, risk is increased for exposures involving a high titer of HIV, prolonged contact, an extensive area, or an area in which skin integrity is visibly compromised. For skin exposures without increased risk, the risk of drug toxicity outweighs the benefit of postexposure prophylaxis. When blood or skin exposure is involved, prophylaxis is not recommended. The exposed worker may be offered zidovudine plus lamivudine. Addition of indinavir is optional (associated with an increased risk of toxicity).

When fluid containing visible blood, other fluid (including semen, vaginal secretions, and cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids), or tissue is involved, prophylaxis is not recommended. The exposed worker may be offered zidovudine plus lamivudine.

When other fluid (e.g., urine) is involved, prophylaxis is not recommended and should not be offered. (Strength of evidence for prophylaxis = C)

Pediatric dosage. Not applicable.

Perinatally acquired HIV infection

Antiretroviral prophylaxis of maternal–infant HIV transmission is indicated when the potential benefits of drug therapy are believed to outweigh the risks to the mother or the infant. The CDC prophylaxis regimen consists of three separate components: antepartum, intrapartum, and neonatal. As many as possible of these components should be used in prophylaxis, depending on the time of identification of eligible patients and the availability of care. Although some form of antiretroviral prophylaxis is recommended or offered in all scenarios, therapy should be instituted only after consultation with the woman and careful discussion of the potential benefits and risks involved. Decisions about the use of antiretroviral drugs during pregnancy should be made only after careful assessment of many factors, including the degree of maternal immunodeficiency (based on CD4+ lymphocyte count), the risk for maternal disease progression (based on viral load measurements), history of prior or current antiretroviral drug therapy, gestational age, and supportive care needs. Decisions about the initiation or continuation of therapy should be based on the same factors used for similar decisions in nonpregnant women, with additional consideration of the risk to the fetus and the infant. Current recommendations stress that the antiviral regimens should be selected with consideration of the proven benefit of antiretroviral therapy for the health of the infected woman as well as the potential reduction in risk of HIV transmission to the child. Ultimately, the final decision to accept or

reject zidovudine treatment recommended for the woman and her child is the right and responsibility of the woman. Recommendations also generally address four scenarios:

1. Pregnant HIV-infected women (with any CD4+ lymphocyte count) who are at 14 weeks' gestation and without a history of extensive (more than six months) antiretroviral therapy: recommend or offer all components of prophylaxis.
2. Pregnant HIV-infected women who have a history of extensive previous antiretroviral therapy before pregnancy: recommend or offer all components of prophylaxis.
3. Pregnant HIV-infected women who have not received antepartum antiretroviral therapy and who are in labor: recommend or offer intrapartum and neonatal components of prophylaxis.
4. Infants born to HIV-infected women who have received no intrapartum antiretroviral therapy: recommend or offer neonatal component of prophylaxis. It is advised that therapy for the infant be initiated as soon as possible (preferably within hours) after delivery. No data support offering antiretroviral therapy to the infant if therapy cannot be initiated within 24 hours after delivery.

Although combination antiretroviral therapy is standard in the general treatment of HIV-infected adults, the additional benefits and risks of combination therapy for prevention of perinatal transmission are as yet undetermined. Although combination regimens are considered optimal for long-term maternal benefits, zidovudine monotherapy is acceptable if the woman wants to minimize exposure of the fetus to other drugs. Because zidovudine is the only drug that has been proven to reduce the risk of perinatal transmission, all combinations of antiretroviral agents should include zidovudine as part of the initial therapeutic regimen. For patients already receiving regimens that do not include zidovudine, the addition of zidovudine or substitution of zidovudine for another nucleoside reverse-transcriptase inhibitor is recommended. Zidovudine should be administered as follows:

- For antepartum prevention, zidovudine 100 mg orally five times daily, initiated at 14–34 weeks' gestation and continued for the remainder of the pregnancy.
- For intrapartum prevention, during labor, zidovudine 2 mg/kg i.v. over one hour, followed by 1 mg/kg/hr i.v. by continuous infusion until delivery.
- Neonatal dosage: zidovudine syrup 2 mg/kg orally every six hours for six weeks, beginning 8–12 hours after birth. (Strength of evidence for prophylaxis = A)

Pediatric dosage. In the case of adolescent pregnancy, the adult recommendations should be used. Additional guidelines for the prevention of perinatal transmission of HIV can be found at http://www.aidsinfo.nih.gov/guidelines/, the Web site of the HIV/AIDS Treatment Information Service.

Perinatally acquired herpes simplex virus (HSV) type 2 infection

The efficacy of prophylactic antivirals in pregnant women with genital HSV infection is not well established, although acyclovir administration has been associated with lower cesarean delivery rates. If prophylaxis is chosen, the recommended regimen is acyclovir 400 mg orally three times daily from 36 weeks' gestation to delivery in primary HSV-infected mothers. An alternative is valacyclovir 1 g (as the hydrochloride) orally twice a day. For mothers with frequently recurring genital HSV (six episodes a year), the recommended regimen is acyclovir 200 mg four times daily for one to four weeks before delivery. Alternatives are famciclovir orally 125 mg twice a day or valacyclovir orally 500 mg (as the hydrochloride) twice a day. Prophylaxis is not recommended in pregnant women with a remote history of genital HSV (no recent recurrence or HSV seropositive). (Strength of evidence for prophylaxis = A for prevention of cesarean delivery in mothers with primary HSV infection and B for recurrent genital HSV. Strength of evidence against prophylaxis = C for mothers with a remote history of genital HSV)

Health care professionals are encouraged to register pregnant women receiving acyclovir with the acyclovir pregnancy registry at 888-825-5249, extension 39441.

Pediatric dosage. According to adult efficacy data, acyclovir is associated with lower cesarean delivery rates in HSV-infected mothers and lower risks inherent in the surgical procedure. Adolescents should receive the adult dosage of acyclovir: acyclovir 400 mg orally three times daily from 36 weeks' gestation to delivery in primary HSV-infected adolescents. An alternative is valacyclovir 1 g (as the hydrochloride) orally twice a day. Acyclovir 200 mg orally four times daily for one to four weeks before delivery is recommended for mothers with frequently recurring genital HSV (six episodes a year). Alternatives are famciclovir orally 125 mg twice a day or valacyclovir orally 500 mg (as the hydrochloride) twice a day. Prophylaxis is not recommended in pregnant adolescents with a remote history of genital HSV (no recent recurrence or HSV seropositive).

Perinatally acquired group B streptococcal infection

Two acceptable strategies for the prevention of perinatal group B streptococcal infection have been proposed by CDC and the American Academy of Pediatrics (AAP)/American College of Obstetricians and Gynecologists (ACOG). The two strategies include screening at 35-37 weeks and using only risk factors. Regardless of the strategy used, women should be given antimicrobial prophylaxis if they had a previous delivery of an infant with group B streptococcal disease or group B streptococcal bacteruria during the pregnancy. The prenatal screening strategy includes screening all pregnant women at 35-37 weeks and offering antimicrobial prophylaxis to all pregnant women with positive group B streptococcal cultures. If the results of group B streptococcal cultures are not known at the time of labor, intrapartum prophylaxis should be administered if one of the following risk factors is present: delivery at <37 weeks' gestation (for ruptured membranes with labor at <37 weeks, group B streptococcal culture should be collected and either antimicrobials given until cultures are completed and negative or antimicrobials begun once positive culture results are available), duration of membrane rupture of ≥18 hours before delivery, or intrapartum fever (≥38 Â°C). The risk-factor strategy is based only on the presence of the preceding

intrapartum risk factors; intrapartum antimicrobial prophylaxis is administered if one or more of these risk factors are present.

The recommendation for intrapartum therapy is penicillin G 5 million units i.v. load, then 2.5 million units i.v. every four hours until delivery. An alternative regimen is ampicillin 2 g (as the sodium) i.v., then 1 g i.v. every four hours until delivery. Patients allergic to penicillin may receive clindamycin 900 mg (as the phosphate) i.v. every eight hours or erythromycin 500 mg (as the lactobionate) i.v. every six hours until delivery. (Strength of evidence for prophylaxis = A)

Pediatric dosage. CDC and AAP have published official recommendations on antimicrobial prophylaxis is of perinatal group B streptococcal infection and empirical management of neonates born to women receiving intrapartum chemoprophylaxis. Readers are referred to the adult recommendation for at-risk patients who require prophylaxis.

Opportunistic infections in afebrile granulocytopenic patients

Bacterial prophylaxis. Prophylaxis is generally not recommended for patients with hematologic malignancies or bone marrow transplantation (BMT) patients who are expected to experience prolonged (seven days or more) granulocytopenia because of the lack of demonstrated improvement in mortality and the risk of drug-resistant bacteria. Exceptions are trimethoprim–sulfamethoxazole for patients at risk (e.g., patients with childhood leukemia, histiocytosis, or AIDS) for P. carinii pneumonitis. The quinolones may be considered for short periods if the potential for resistant organisms is appreciated and outweighed by the benefits. The dosage is trimethoprim 160 mg and sulfamethoxazole 800 mg orally twice daily. If quinolones are used, the dosage is ciprofloxacin 500 mg orally twice daily, ciprofloxacin 400 mg (as the lactate) i.v. twice daily, or ofloxacin 200 mg orally or i.v. twice daily. Prophylaxis should start when antineoplastic therapy begins for patients with hematologic malignancies and from the start of the conditioning regimen for BMT patients. Prophylaxis should continue until the granulocyte count exceeds 500/mm^3 or until fever occurs. If fever occurs, presumptive therapy with an appropriate antimicrobial should be initiated. (Strength of evidence against prophylaxis = C)

Pediatric dosage in bacterial prophylaxis. Prophylaxis is not recommended for pediatric patients with hematologic malignancies or BMT patients who are expected to experience prolonged (seven days or more) granulocytopenia because of the lack of demonstrated improvement in mortality and the risk of drug-resistant bacteria. Exceptions are trimethoprim–sulfamethoxazole for pediatric patients at risk (e.g., patients with childhood leukemia, histiocytosis, or AIDS) for P. carinii pneumonitis. The regimen is trimethoprim 6–10 mg/kg/day and sulfamethoxazole 30–50 mg/kg/day divided twice daily. Prophylaxis should start when antineoplastic therapy begins for patients with hematologic malignancies and from the start of the conditioning regimen for BMT patients. Prophylaxis should continue until the granulocyte count exceeds 500/mm^3 or until fever occurs. Although children have been treated with ciprofloxacin without the occurrence of arthropathy, further safety data are needed before widespread use can be recommended in this patient population. Norfloxacin has also been used safely in children, but data are limited.

Fungal prophylaxis. Fungal prophylaxis is generally not recommended for patients with hematologic malignancies or BMT patients who are expected to experience prolonged (seven days or more) granulocytopenia. However, if the risk of C. albicans infection is high and the risk of infection with other Candida species is low, fluconazole may be an option. The significant risks (increasing the prevalence of non-albicans Candida species and other more resistant fungal infections) and the associated costs should be considered. The dosage is fluconazole 400 mg orally or i.v. once daily. An alternative is i.v. amphotericin B 0.1–0.25 mg/kg/day. Prophylaxis should start when antineoplastic therapy begins for patients with hematologic malignancies and from the start of the conditioning regimen for BMT patients. Prophylaxis should be continued until the granulocyte count exceeds 500/mm^3 or until fever occurs. (Strength of evidence against prophylaxis = C)

Pediatric dosage in fungal prophylaxis. Fungal prophylaxis is not recommended for pediatric patients with hematologic malignancies or BMT patients who are expected to experience prolonged (seven days or more) granulocytopenia. However, if the risk of C. albicans infection is high and the risk of infection with other Candida species is low, fluconazole may be an option. The significant risks (increasing the prevalence of non-albicans Candida species and other more resistant fungal infections) and the associated costs should be considered. The dosage is fluconazole 3–5 mg/kg/day orally or i.v. for fungal prophylaxis. An alternative is i.v. amphotericin B 0.1–0.25 mg/kg/day. Prophylaxis should start when antineoplastic therapy begins for patients with hematologic malignancies and from the start of the conditioning regimen for BMT patients. Prophylaxis should be continued until the granulocyte count exceeds 500/mm^3 or until fever occurs.

Viral prophylaxis. Although antiviral therapy for secondary prophylaxis (suppressive therapy) is acceptable in BMT patients, antiviral therapy for primary prophylaxis is not recommended for granulocytopenic patients, including BMT patients. (Strength of evidence against primary prophylaxis = C)

Pediatric dosage in viral prophylaxis. Primary prophylaxis is not recommended for granulocytopenic pediatric patients, including BMT patients.

Opportunistic infections in HIV-infected persons

Combination antiretroviral drug regimens, particularly those containing protease inhibitors, are capable of increasing CD4+ lymphocyte counts by as many as 100–250 cells/m L over baseline values at the initiation of therapy. Although studies are currently being conducted, it is not yet known whether these increases in CD4+ lymphocytes induced by antiretroviral therapy are sufficient to restore immune function to the degree that drug therapies providing prophylaxis against opportunistic infections may be discontinued. Current data are insufficient to indicate whether these patients are no longer at high risk even though their CD4+ lymphocytes were significantly depleted at an earlier time. Most experts recommend that, until such data become available, prophylactic therapies be initiated on the basis of the lowest documented CD4+ lymphocyte count and that prophylactic therapies be continued regardless of subsequent therapy-induced increases in the CD4+ lymphocyte counts.

Candidiasis, histoplasmosis, and coccidioidomycosis in HIV-infected persons

Candida. Routine primary prophylaxis of mucocutaneous Candida infections is not recommended for HIV-infected adults because of the effectiveness of therapy for acute disease, infrequent occurrence of serious invasive disease, questionable mortality benefits of prophylaxis, concerns about the development of azole-resistant Candida species, potential for multiple drug interactions involving the azole antifungals, and costs of routine prophylaxis. Azole antifungal agents may be used in patients at high risk of infection (i.e., CD4+ lymphocyte count of <50 cells/m L), but these patients should be very carefully selected and therapy instituted on an individual basis and only in unusual circumstances. If primary antifungal prophylaxis is to be initiated, oral fluconazole 100–200 mg every day is preferred. Although itraconazole has been shown to be effective in the treatment of acute candidiasis, this drug has not yet been clearly demonstrated to be effective as a prophylactic agent, and use of itraconazole is not recommended for this purpose.

Disseminated histoplasmosis or coccidioidomycosis. Routine prophylaxis in HIV-infected adults is not recommended for disseminated histoplasmosis or coccidioidomycosis. In addition to the lack of substantive data on prophylaxis, the potential development of azole-resistant fungal strains and cost-effectiveness of prophylaxis are concerns that should discourage routine practice. Prophylactic use of azole antifungal agents, specifically itraconazole 200 mg orally every day, may be considered for patients with advanced HIV infection (CD4+ lymphocyte count of <100 cells/m L) who live in endemic areas. Patients should be carefully selected on a case-by-case basis; prophylaxis should not be routinely instituted. The oral bioavailability of itraconazole capsules has been shown to be approximately 50% lower in persons with AIDS than in healthy volunteers. In contrast, the administration of itraconazole oral solution to persons with AIDS has been shown to achieve plasma levels approximately 50–70% higher than those achieved after administration of the oral capsule. Therefore, the oral solution may be the preferred dosage form if itraconazole is to be administered in this population. (Strength of evidence against prophylaxis = B)

Pediatric dosage. Candida. Routine primary prophylaxis of mucocutaneous Candida infections is not currently recommended for children. Antifungal agents may be used in patients at high risk of infection (i.e., CD4+ lymphocyte count of <750 cells/m L for children less than one year of age, <500 cells/m L for children one to five years of age, and <200 cells/m L for children six years of age or older), but these patients should be carefully selected and therapy instituted on an individual basis. Antifungal agents include nystatin (100,000 units/m L) 4–6 mL orally every six hours and topical clotrimazole 10 mg orally five times a day. The use of azole antifungal agents is not recommended in the pediatric population.

Disseminated histoplasmosis or coccidioidomycosis. Routine prophylaxis of disseminated histoplasmosis or coccidioidomycosis in HIV-infected children is not recommended. Prophylactic use of azole antifungal agents (fluconazole 3–6 mg/kg orally every day or itraconazole 2–5 mg/kg orally every 12–24 hours) may be considered for patients with advanced HIV infection (i.e., CD4+ lymphocyte count of <750 cells/m L for children less than one year of age, <500 cells/m L for

children one to five years of age, and <200 cells/m L for children six years of age or older) who live in endemic areas. Patients should be carefully selected on a case-by-case basis; prophylaxis should not be routinely instituted.

Cryptococcus neoformans infections in HIV-infected persons

In the absence of demonstrated survival benefits for prophylaxis and given the concerns about development of azole-resistant strains and cost-effectiveness, prophylaxis of cryptococcal disease should not be routinely recommended for HIV-infected adults. If prophylaxis is to be used, the recommended regimen is fluconazole 200 mg orally every day. Although itraconazole 200 mg orally every day is recommended by CDC as an alternative to fluconazole, at least one clinical study has shown fluconazole to be superior to itraconazole in this setting. Patients should be carefully selected on an individual basis and should be evaluated for factors that may place them at high risk of infection (CD4+ lymphocyte count of <50 cells/m L and residence in an endemic geographic area). (Strength of evidence against prophylaxis = A)

Pediatric dosage. Primary prophylaxis for cryptococcal disease in pediatric patients is not recommended. As is the case for adults, there are no data on the value of routine prophylaxis of HIV-infected children. Prophylactic use of azole antifungal agents (fluconazole 3–6 mg/kg orally every day or itraconazole 2–5 mg/kg orally every 12–24 hours) may be considered for patients with advanced HIV infection (i.e., CD4+ lymphocyte count of <750 cells/m L for children less than one year of age, <500 cells/m L for children one to five years of age, and <200 cells/m L for children six years of age or older) who live in endemic areas. However, patients should be carefully selected on a case-by-case basis; prophylaxis should not be routinely instituted.

Disseminated Mycobacterium avium complex (MAC) infection in HIV-infected persons

Prophylaxis against MAC in HIV-infected adults is recommended when the CD4+ lymphocyte count is <50–75 cells/m L. The recommended regimen is oral azithromycin 1200 mg weekly or oral clarithromycin 500 mg twice daily. Rifabutin 300 mg every day orally, either alone or in combination with azithromycin, is recommended as an alternative agent. Selection of a specific agent should be based on individual patient characteristics and concurrent medications. (Strength of evidence for prophylaxis = A)

Pediatric dosage. Although prophylaxis of MAC infection in children has not been rigorously evaluated, primary prophylaxis is presumed to be effective and is recommended in the following groups of children: six years of age or older with a CD4+ lymphocyte count of <50 cells/m L, two to six years of age with a CD4+ lymphocyte count of <75 cells/m L, one to two years of age with a CD4+ lymphocyte count of <500 cells/m L, and less than one year of age with a CD4+ lymphocyte count of <750 cells/m L. Oral azithromycin 20 mg/kg (up to a maximum of 1200 mg) once each week or clarithromycin 7.5 mg/kg (up to a maximum of 500 mg) every 12 hours is the preferred regimen for prophylaxis in these groups. Azithromycin 5 mg/kg (up to a maximum of 250 mg) every day may be used as an alternative. Rifabutin 300 mg every day orally for children 6–12 years old and 5 mg/kg every day orally for children less than 6 years old is

recommended as an alternative agent when clarithromycin and azithromycin are poorly tolerated.

P. carinii pneumonia (PCP) in HIV-infected persons

Primary prophylaxis against PCP in adults is indicated for patients at high risk (HIV-infected adults with CD4+ lymphocyte counts of less than or equal to 200 cells/m L, unexplained fever of 100 Â°F for two or more weeks, or a history of oropharyngeal candidiasis). Trimethoprim 160 mg and sulfamethoxazole 800 mg orally every day is the recommended regimen. Alternatives are trimethoprim 80 mg and sulfamethoxazole 400 mg orally every day, trimethoprim 160 mg and sulfamethoxazole 800 mg orally three times a week, dapsone 50 mg orally twice daily or 100 mg orally every day, dapsone 50 mg orally every day plus pyrimethamine 50 mg orally every week plus leucovorin 25 mg (as the calcium) orally every week, dapsone 200 mg orally every week plus pyrimethamine 75 mg orally every week plus leucovorin 25 mg orally every week, and aerosolized pentamidine isethionate 300 mg/month by Respirgard II nebulizer (Marquest Medical Products). (Strength of evidence for prophylaxis = A)

Pediatric dosage. Children born to HIV-infected mothers should be administered prophylaxis beginning at four to six weeks of age; prophylaxis should be discontinued if the child is subsequently determined to be HIV-negative. The need for prophylaxis after the age of 12 months is determined on the basis of age-specific CD4+ lymphocyte counts. PCP prophylaxis is indicated for children one to five years of age in whom the CD4+ lymphocyte count falls to less than or equal to 500 cells/m L or a CD4+ lymphocyte percentage of <15%. In children 6–12 years of age, PCP prophylaxis is indicated for CD4+ lymphocyte counts of less than or equal to 200 cells/m L or a CD4+ lymphocyte percentage of <15%.

Trimethoprim 150 mg/m^2/day and sulfamethoxazole 750 mg/m^2/day in two divided doses orally three times a week on consecutive days is the preferred regimen in all children between the ages of one month and five years. Alternative dosages are not proven to be effective in this age group and are not recommended. Children 6–12 years of age may receive the preferred regimen administered in a single daily dose; an alternative schedule in this age group is the same dose given daily in two divided doses, or two divided doses three times a week on alternate days. Children unable to tolerate trimethoprim–sulfamethoxazole should receive dapsone 2 mg/kg (not to exceed 100 mg) every day orally, aerosolized pentamidine isethionate 300 mg every month for children five years old or older, or pentamidine isethionate i.v. 4 mg/kg every two to four weeks.

Toxoplasmic encephalitis (TE) in HIV-infected persons

Primary prophylaxis against TE in all HIV-infected adults is not routinely recommended. Rather, prophylaxis should be reserved for carefully selected high-risk patients with advanced disease. Avoiding exposure to T. gondii is an important aspect of disease prevention. Because the risk of acquiring new strains of Toxoplasma is unknown, seropositive and seronegative persons who are infected with HIV should be advised about preventive practices. These include eating red meats only if they have been well cooked; practicing hand washing after gardening, yard work, or other outdoor activities; and, if there is a cat in the

household, changing the litter box daily to prevent maturation of infectious oocysts.

Primary prophylaxis against TE is indicated only for HIV-infected patients with advanced disease (CD4+ lymphocyte counts of <100 cells/m L) who are also immunoglobulin G seropositive for T. gondii. Trimethoprim 160 mg and sulfamethoxazole 800 mg orally every day is the preferred regimen for all patients who are able to tolerate the drug. Alternative dosages are trimethoprim 80 mg and sulfamethoxazole 400 mg orally every day and trimethoprim 160 mg and sulfamethoxazole 800 mg orally three times a week. Dapsone 50 mg orally every day plus pyrimethamine 50 mg every week is an acceptable alternative regimen in patients unable to tolerate trimethoprim–sulfamethoxazole. Leucovorin 25 mg (as the calcium) orally every week may also be administered with this regimen to prevent hematologic toxicity. Dapsone alone, pyrimethamine alone, and aerosolized pentamidine are not recommended as alternative regimens because of insufficient efficacy data or demonstrated inferior efficacy. (Strength of evidence against primary prophylaxis = A)

Pediatric dosage. Primary prophylaxis against TE in HIV-infected pediatric patients is not recommended. In children with immunoglobulin G antibody seropositive to T. gondii and a CD4+ lymphocyte count indicating severe immunosuppression (<12 months of age with CD4+ lymphocyte counts of <750 cells/m L or a CD4+ lymphocyte percentage of <15%, 1–5 years of age with a CD4+ lymphocyte count of <500 cells/m L or a CD4+ lymphocyte percentage of <15%, or 6–12 years of age with a CD4+ lymphocyte count of <200 cells/m L or a CD4+ lymphocyte percentage of <15%), secondary prophylaxis may be an option and should be administered with trimethoprim 150 mg/m^2/day and sulfamethoxazole 750 mg/m^2/day orally every day. An alternative regimen for children one month old and older is dapsone 2 mg/kg or 15 mg/m^2 (not to exceed 25 mg) orally every day plus pyrimethamine 1 mg/kg orally every day plus leucovorin 5 mg (as the calcium) orally every three days.

Cytomegalovirus (CMV) disease in HIV-infected persons

Primary prophylaxis of CMV disease is not routinely recommended because of insufficient data demonstrating clinical efficacy versus benefits and concerns about the development of drug-resistant CMV strains during long-term antiviral use. The use of oral ganciclovir 1000 mg three times a day has been recommended in carefully selected patients who are seropositive for antibodies to CMV and have advanced HIV infection (CD4+ lymphocyte count of <50 cells/m L). (Strength of evidence against primary prophylaxis = B)

Pediatric dosage. Primary prophylaxis against CMV is not recommended for pediatric patients. Primary prophylaxis with ganciclovir may eventually be an option for patients who are seropositive for antibodies to CMV and have severe immunosuppression. Although currently under study, the efficacy of oral ganciclovir for primary prophylaxis is not yet demonstrated to be beneficial in children and is not recommended at this time.

Herpes simplex and varicella-zoster virus (VZV) infections in HIV-infected persons

Primary chemoprophylaxis for HSV and VZV is not recommended. Because severe HSV disease in all age groups is a result of reactivation rather than primary infection, and because HSV-2 reactivation is much more problematic than HSV-1, prophylaxis efforts are directed toward prevention of primary infections in persons seronegative for antibodies to HSV-2. This is most effectively accomplished through the use of latex condoms by sexually active HIV-infected adults rather than chemoprophylaxis. HIV-infected persons with no reliable history of VZV infection or documented seronegativity for antibodies to VZV are possibly susceptible to primary infection and should avoid exposure to individuals with either varicella or herpes zoster.

Because of the increased severity of primary VZV infection in HIV-infected adults, susceptible persons should be administered varicella-zoster immune globulin (VZIG) after significant exposure to persons with active varicella or herpes zoster. For detailed information on immunoprophylaxis, readers are referred to the CDC guidelines. No other forms of prophylaxis are indicated. (Strength of evidence against primary prophylaxis = C)

Pediatric dosage. Primary chemoprophylaxis for HSV and VZV is not recommended for pediatric patients. Because of the higher severity of primary VZV infection in HIV-infected children, susceptible persons should be administered VZIG after significant exposure to persons with active varicella or herpes zoster. For detailed information on immunoprophylaxis, readers are referred to the CDC guidelines. No other forms of prophylaxis are indicated.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Each recommendation is assigned a category corresponding to the type and strength of evidence. The recommendations are based on a comprehensive review of the literature or on a consensus of the panel based on the clinical experience of the individual panel members and a paucity of quality supporting literature. Where opinions were markedly divided, recommendations indicate that a substantial number of panel members supported an alternative approach.

In most cases the pediatric recommendations have been extrapolated from the adult data. Because pediatric trials have generally not been conducted, a strength of evidence has not been applied to these recommendations.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

The potential benefits of recommended antimicrobial prophylactic regimens prevention of primary infection are summarized for the following conditions:

- Endocarditis: The evidence supporting the use of prophylactic antimicrobials for high-risk patients with cardiac lesions before medical or dental procedures that produce bacteremia is incomplete but suggests that the benefits of prophylaxis against endocarditis outweigh the risks and costs for these patients.
- Influenza A: Double-blind, placebo-controlled clinical trials have demonstrated that the prophylactic effectiveness of amantadine and rimantadine is similar. Amantadine and rimantadine were highly effective in preventing influenza-like illness; the rate of illness was 78% and 65% lower, respectively, compared with placebo. The efficacy rates for prevention of laboratory-documented influenza were 91% for amantadine and 85% for rimantadine.
- Malaria: Various drug regimens and combinations have been shown in randomized controlled clinical trials to be effective in preventing malaria infection. These are discussed in detail in the guideline document.
- Tuberculosis: Isoniazid prophylaxis can reduce the risk of tuberculosis (TB) by more than 90% in infected persons who adhere to therapy. The efficacy of isoniazid preventive therapy in HIV-infected persons has been investigated only in small trials; however, the drug appears to confer protection.
- Occupational Exposure to HIV: Evaluation of zidovudine in humans is difficult because the low occurrence of HIV seroconversion after occupational exposure necessitates a very large sample to demonstrate a prophylactic effect. Because well-controlled trials of chemoprophylaxis after occupational exposure have not been conducted recommendations were extrapolated from trials in patients with HIV infection. Refer to the guideline document for further discussion of the efficacy and risks associated with postexposure prophylaxis.
- Perinatally acquired HIV infection: The AIDS Clinical Trials Group Protocol 076 demonstrated that the relative risk of maternal–infant transmission was 67.5% lower with zidovudine than with placebo (8.3% and 25.5%, respectively). Subsequent studies have similarly demonstrated differences in transmission between no prophylaxis (19–29%) and zidovudine monotherapy (3–14%).
- Perinatally acquired herpes simplex virus type 2 infection: The efficacy of prophylaxis with acyclovir in the prevention of HSV disease in newborns is not known; however, use of this regimen has been associated with a lower rate of cesarean deliveries. The limited available data on the efficacy of prophylaxis to prevent HSV-2 are discussed in greater detail in the guideline document.
- Perinatally acquired group B streptococcal infection: Several randomized trials have demonstrated that intrapartum administration of antimicrobials is effective in reducing the rate of vertical transmission of group B streptococci. In one study, the frequency of early-onset group B streptococcal disease was significantly different in the infants whose mothers received prophylaxis (0%) compared with those who received no treatment (6.3%). In a meta-analysis of controlled trials and cohort studies, the use of antimicrobial prophylaxis was associated with a 30-fold lower frequency of early-onset group B streptococcal infection.
- Opportunistic infections in HIV-infected persons: The prophylaxis and treatment of opportunistic infections in HIV-infected patients is a rapidly changing area of infectious diseases. Refer to the guideline document for detailed discussion of the benefits associated with various prophylactic regimens, that reflects the available clinical information that was current at the time the guideline was prepared.

Refer to the guideline document for further discussion of the efficacy of recommended prophylactic regimens, discussion of risk-benefit considerations for other prophylactic regimens, and discussion of efficacy data available at the time of publication for pediatric populations.

POTENTIAL HARMS

- Prophylactic antimicrobial regimens are associated with adverse effects; however, discussion of the adverse-effect profile of each specific antimicrobial is beyond the scope of these guidelines.
- Because most occupational exposures to HIV do not result in seropositivity, potential toxicity should be considered when postexposure prophylaxis is prescribed. One third of health care workers in two surveillance studies prematurely discontinued zidovudine because of adverse effects.
- When considering the use of antimicrobial for prophylaxis, one must also consider the risks of contributing to the development of antimicrobial resistance.

Refer to the guideline document for further discussion of risk-benefit considerations for prophylactic regimens and regimen-specific considerations for the risk of emergence of resistant strains.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

1. Clinical studies to determine the optimal dosages of antimicrobials used for pediatric prophylaxis are essentially nonexistent. The pediatric dosages provided in the guideline document are based largely on pharmacokinetic equivalence and the generalization of the adult efficacy data to pediatric patients.
2. The recommendations in this document may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgment of the clinician and consideration of individual patient circumstances and available resources.
3. These guidelines reflect current knowledge (at the time of publication) on nonsurgical antimicrobial prophylaxis. Given the dynamic nature of scientific information and technology, periodic review, updating, and revision are to be expected.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

American Society of Health-System Pharmacists. ASHP therapeutic guidelines for nonsurgical antimicrobial prophylaxis. American Society of Health-System Pharmacists. Am J Health Syst Pharm 1999 Jun 15;56(12):1201-50. [377 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Jun 15

GUIDELINE DEVELOPER(S)

American Society of Health-System Pharmacists - Professional Association

SOURCE(S) OF FUNDING

American Society of Health-System Pharmacists (ASHP)

GUIDELINE COMMITTEE

- American Society of Health-System Pharmacists (ASHP) Commission on Therapeutics
- Rocky Mountain Poison and Drug Center under contract to ASHP

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Panel members and contractors were required to disclose any possible conflicts

GUIDELINE STATUS

This is the current release of the guideline. It supersedes a previously issued version (ASHP therapeutic guidelines on nonsurgical antimicrobial prophylaxis. ASHP Commission on Therapeutics. Am J Hosp Pharm. 1990 Jul;47(7):1618-21).

These guidelines reflect current knowledge (at the time of publication) on nonsurgical antimicrobial prophylaxis. Given the dynamic nature of scientific information and technology, periodic review, updating, and revision are to be expected.

American Society of Health-System Pharmacists (ASHP) guidelines are reviewed and revised as needed, generally every three to five years.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Society of Health-System Pharmacists (ASHP) Web site.

Print copies: Available from the American Society of Health-System Pharmacists, 7272 Wisconsin Avenue, Bethesda, MD 20814.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on April 10, 2000. It was verified by the guideline developer on August 4, 2000.

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